REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-18 are in this Application. Claims 9-16 have been withdrawn from consideration. Claims 1-8 have been rejected under 35 U.S.C. § 112. Claims 1-4 have been rejected under 35 U.S.C. § 102(b). Claims 1-3 have been rejected under 35 U.S.C. § 102(e). Claims 1-3, 7 and 8 have been rejected under 35 U.S.C. § 103(a). New claims 19-23 have now been added. Claim 1 has been amended herewith.

Specification Objections

Replacement paragraph indicating the patent lineage, including the corrected status of the parent application is provided herewith.

Claims Objections

Claim 1 has been amended to correct typographical errors noted by the Examiner.

35 U.S.C. § 112, 1st paragraph Rejections

The Examiner has rejected claims 1-8, 17 and 18 under 35 USC 112, 1st paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventor had possession of the claimed invention. Applicant respectfully traverses the Examiner's rejections. Claims 2 and 3 have been canceled, rendering moot the Examiner's rejection thereof. Claim 1 has now been amended.

The Examiner has based the rejection of claims 1-8 and 17-18 on the allegation that the specification fails to demonstrate the truly benign nature of the mitigating traits on cultivated crops transformed therewith. Applicant strongly disagrees.

On page 4 of the communication of August 1, the Examiner has alleged that the demonstration that the transformed dwarf tobacco and transformed dwarf Brassica were inefficient competitors with the wild-type tobacco or Brassica indicates that the transformed tobacco and Brassica plants ***did not have benign traits***. Applicants believe that the Examiner has misunderstood the experimental design.

In Examples 1 and 2, transgenic TM tobacco (Example 1) and *Brassica* (oilseed rape) (Example 2) plants were produced by artificial introgression (by

transformation) of a tandem construct containing an *ahas*^{R} (acetohydroxy acid synthase) gene (GenBank Accession No. X51514) for herbicide resistance as the primary desirable gene, and the dwarfing Δ*gai* (gibberellic acid-insensitive) mutant gene as a mitigator. The plants were grown under "cultivated" conditions (exclusively TM plants, with regular spacing, as in a field planted with a crop), to simulate conditions of intentional crop growth, and under "uncultivated" conditions (TM plants grown together with wild type plants, variety of spacing) to simulate uncontained, unintended growth. Applicant wishes to point out that the "cultivated" conditions are designed to eliminate competition (identical plants, regular spacing), while the "uncultivated" conditions are designed to simulate plants having the tandem TM constructs having escaped containment, growing unintentionally under "weedy" conditions (TM plants grown along with wild type, irregular spacing).

In Example 1, phenotypes of tobacco plants grown under "cultivated" and "uncultivated" conditions were compared, according to chlorophyll content, stem thickness, internode length, canopy size and shape, size, color and longevity of leaves, mass per unit area of leaves, number of apical branches and number of flowers. Vegetative fitness (based on plant height) and reproductive fitness (based on flower and fruit number formed per m^2) of TM plants relative to wild type, were calculated at the different spacings and time intervals as a TM/wild type ratio.

> "All the T_0 lines had similar semi-dwarf phenotypes, with thicker stems, shorter internodes, compact canopy, more leaves that were darker green and felt thicker (and had a greater mass per unit area), and had more apical branches and flowers than those of the wild type."
>
> "The dwarf and imazapyr resistant TM transgenic hybrid tobacco plants (simulating a TM introgressed hybrid) were more productive than the wild type when cultivated alone. They formed many more flowers than the wild type, which is an indication of a higher harvest index (Figure 2). Conversely, the TM transgenics were weak competitors and highly unfit when co-cultivated with the wild type in ecological simulation competition experiments (Figures 2,3). The lack of flowers on the TM plants in the competitive situation (Figure 2) led to a zero reproductive fitness of the TM plants grown in a 1:1 mixture with the wild type at the spacings used, which are representative of those of weeds in the field (Figure 2). The highest vegetative fitness was less

than 30% of the wild type (Figure 3)."(page 63, lines 19-29 of the instant specification)

Thus, the transgenic TM hybrid tobacco plants, when grown alone (as a crop) in "cultivated" conditions, were **more productive and produced many more flowers than wild type tobacco plants grown alone**. When grown together with wild type tobacco plants (simulating uncontained, "weedy" growth) in "uncultivated" conditions, however, the transgenic TM hybrid plants had **zero reproductive fitness and strongly reduced vegetative fitness**, i.e., competed poorly with the co-cultivated wild type plants.

In Example 2, phenotypes of Brassica plants grown under "cultivated" and "uncultivated" conditions were compared, according to plant height, number of leaves, number of stem branches, stem thickness, leaf internode spacing, fresh weight of shoots and roots, lifetime seed production, number of seed-bearing siliques, number of fully developed seeds per silique, number of seeds per plant, quality of seeds, total weight of developed seeds per plant, dry weight of shoots per plant and harvest index. Vegetative fitness (based on plant height) and reproductive fitness (based on the total seed number formed per plant and the total seed output/biotype/unit area) of TM hybrids or BC was calculated relative to wild type *B. campestris* plants.

"The transgenic TM plants had also more abundant, darker green, and thicker leaves, and thicker stems than those of the non-transgenic biotypes (Figure 7). The transgenic TM crops were more productive than the non-transgenic plants when grown alone, and the dry weight of total fully developed seeds per TM plant was greater than that of the non-transgenics."

"Both the transgenic TM heterozygous and homozygous transgenic *B. napus* plants were weak competitors when co-cultivated with the non-transgenic crop plants in ecological competition experiments (Figure 8). By the time the non-transgenics had finished flowering and formed many siliques, all the surviving TM plants cultivated at 2.5-cm spacing failed to flower and had formed only very small canopies, indicating that the reproductive fitness of the TM plants was much lower than that of the non-transgenic competing plants."

"However, both the weakly flowering and the non-flowering transgenic TM plants failed to produce mature siliques or viable seeds.

> "In oilseed rape, unlike in tobacco, the Δ*gai* dwarfism gene is active at the rosette stage, and does not seem to act when the plants start bolting. The TM plants were fertile"(page 73, lines 10-29 of the instant specification)

Thus, the transgenic TM hybrid Brassica plants, when grown alone (as a crop) in "cultivated" conditions, were **more productive and has a greater dry weight of fully developed seeds per plant than wild type Brassica plants grown alone**. When grown as together with wild type B. campestris plants (uncontained, "weedy" conditions) in "uncultivated" conditions, however, the transgenic TM plants had **zero reproductive fitness and strongly reduced vegetative fitness**, i.e., competed poorly with the co-cultivated wild type B. campestris plants.

Thus, expression of the dwarfing Δ*gai* mutant gene was **truly benign** or advantageous for both the transgenic TM tobacco and transgenic TM Brassica when grown under "cultivated", crop conditions (both TM tobacco and TM Brassica outperformed identical but untransformed plants when grown alone). However, under "uncultivated" conditions (simulating unintentional, uncontained growth, introgression or weedy transformation), expression of the dwarfing Δ*gai* mutant gene was clearly detrimental to vegetative and reproductive fitness of the transgenic TM plants, effectively preventing competition with their co-cultivated wild type plants. Thus, it is clear that the tandem construct of a herbicide resistance gene with a dwarfing transgenic mitigation gene is advantageous to a crop growing alone, while disadvantageous to the same plant, or a crop-weed hybrid growing in a competitive environment. It will be noted that similar dwarfing, performed genetically, is the basis of the highly touted "Green Revolution" with such dwarf crops cultivated on millions of hectares for the past three decades, with greatly enhanced yields. Indeed, the "Green Revolution" crop plants are incapable of competing outside of agronomic cultivation.

Yet further, introduction of the *Arabidopsis* "shatterproof" gene as a second mitigator sequence into *brassica*, designed to further inhibit undesirable spread of advantageous traits by random introgression into undesirable species, was successful in overcoming the high levels of seed shattering characteristic of wild *brassica* and

producing transgenic plants having uniform seed dispersal (page 73, lines 1-13 of the instant specification).

Further, the Examiner has asserted that the claims are not drawn on particular coding sequences, and no guidance is provided for the sequences responsible for conferring advantageous or mitigating traits.

Applicant wishes to point out that the claimed method is drawn on transforming plants with both advantageous and conditionally disadvantageous, mitigating traits. A detailed, representative listing of examples of tandem constructs having both the advantageous and mitigating traits in tight genetic linkage, wherein the mitigating trait(s) are disadvantageous to the uncultivated interbreeding species related to the cultivated crop is provided in Table 4 (page 54 of the instant specification) and throughout the specification.

Applicant wishes to point out that Table 2 (pages 20-22 of the instant specification), Table 3 (pages 22-23 of the instant specification), Table 5 (pages 74-76 of the instant specification), Table 6 (page 81 of the instant specification); Table 7 (pages 86-87 of the instant specification) and Table 8 (pages 90-91 of the instant specification) list numerous advantageous traits for cultivated crop transformation, and the gene sequences or sources thereof useful for transformation. Suitable mitigating traits, and the sequences thereof, to be used in tight genetic linkage with the advantageous traits, are disclosed in detail in the instant specification, for example, secondary dormancy (see page 43, line 29- page 44, line 27), uniform ripening/anti-shattering (see page 46, line 28- page 47, line 28), dwarfing (see page 47, line 29-page 48, line 28), and bolting (see page 48, line 29-page 49, line 17. Specific mitigating sequences disclosed include, for example, *"shatterproof"*; gai; O,GRF1; phytochrome B, brassinosteroids, and GA_1 and GA_4. Further, mitigating sequences and constructs uniquely suited for individual crops are described (see Example 1 for tobacco, Example 2 for oilseed rape, Example 3 for corn, Example 4 for rice, Example 5 for root crops and Example 6 for trees).

The abovementioned notwithstanding, and in order to expedite prosecution in this case, Applicants have chosen to amend claim 1 to include the limitations of now canceled claims 2 and 3: "wherein said advantageous genetic trait is selected from the group consisting of herbicide resistance, disease, insect and nematode resistance,

environmental stress resistance, high productivity, modified agronomic quality, enhanced yield, modified ripening, bioremediation, expression of heterologous products and genetically modified plant products." and "wherein said at least one mitigating genetic trait is selected from the group consisting of anti-seed shattering, abolished secondary dormancy, dwarfism, uniform or delayed ripening, seed stalk bolting, seed coat defects, uniform germination, root storage promotion, biennial growth, non-flowering and sterility", respectively, thereby further clarifying the claimed method.

In view of the numerous examples of "advantageous" and "mitigating" traits, and methods for their use disclosed in the instant specification, identification, isolation and evaluation of genes conferring "mitigating" traits would not require undue experimentation by one of ordinary skill in the art.

Thus, the Applicant respectfully requests withdrawal of the 35 U.S.C. 112, 1st paragraph rejections.

35 U.S.C. § 112, 2nd paragraph Rejections

The Examiner has rejected claims 1-8, 17 and 18 under 35 USC 112, 2nd paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to make and/or use the claimed invention. Applicant respectfully traverses the Examiner's rejections. Claims 2 and 3 have been canceled, rendering moot the Examiner's rejection thereof. Claim 1 has now been amended.

The Examiner has alleged that in reducing the claimed method to practice, the inventors have not demonstrated that the sequences evaluated were actually benign to crop plants.

The Examiner has based this allegation on the statement that "both the transformed dwarfed tobacco and the transformed dwarf Brassica were inefficient competitors with wild-type tobacco or Brassica...Both homozygous transgenic tobacco and homozygous transgenic Brassica failed to produce flowers as well". While it is correct that Examples 1 and 2 demonstrate that transformed TM tobacco and transformed TM Brassica are inefficient competitors with wild-type tobacco or Brassica under uncultivated conditions, as clearly explained herein (see USC 112, 1st paragraph, *supra*), the same Examples provide crystal clear, irrefutable evidence of

the **truly benign**, and even advantageous effects of co-expression of the advantageous and mitigating dwarf trait in both TM tobacco and TM Brassica *when grown as a crop* (under "cultivated" conditions).

Yet further, the Examiner has correctly noted that TM dwarfed Brassica plants, having poor seed production, would be at a disadvantage when planted in a field with vigorous weeds or when mixed with non-transgenic seeds. Such a disadvantage under these non-cultivated conditions is the essence of the claimed method- "A method of obtaining **a transformed, cultivated crop** capable of mitigating the effects of introgression of at least one advantageous genetically engineered trait to an uncultivated interbreeding species related to the transformed cultivated crop", since, by definition, a cultivated crop is not grown in a field with vigorous weeds (as a result of cultivation techniques and herbicides) or when mixed with any significant amounts of non-transgenic seeds (seed uniformity and quality control is rigorous and routine in modern agriculture).

Regarding Examples 3-4, Applicant wishes to point out that the requirement for enablement may be satisfied with "working" or "prophetic" examples (see MPEP 2164.02). However, detailed Examples 3-4 are presented along with the working examples of successful mitigation of unintended introgression of desirable traits using transgenic TM tobacco and Brassica plants transformed according to the methods of claimed invention, while COLD SPRINGS HARBOR, as noted in the previous response, discloses no working examples, and *only* prophetic examples. Thus, the instant specification discloses representative examples, working and prophetic, of crops transformed with a tandem TM construct and capable of mitigating the effects of introgression of at least one advantageous genetically engineered trait to an uncultivated interbreeding species related to the transformed cultivated crop.

In view of the arguments and amendments provided hereinabove, the Applicant respectfully requests withdrawal of the 35 U.S.C. 112, 1st paragraph rejections.

35 U.S.C. § 102(e) Rejections: LEE et al. (US 5,948,956)

The Examiner has rejected claims 1-3 under 35 USC§102(e), as being anticipated by LEE et al (US 5,948,956). Claims 2 and 3 have been canceled,

rendering moot the Examiner's rejection thereof. Claim 1 has now been amended. The Examiners rejections are respectfully traversed.

The Examiner asserts that Lee et al. teach methods for transforming cultivated turfgrass plants with both an herbicide resistance gene and a second gene conferring male sterility or dwarfism. Applicant disagrees.

Claim 1 has been amended to include the limitation of transforming the crop plant with both an advantageous genetically engineered trait and a mitigating genetic trait having a genetic distance of no greater than 10 centimorgans from each other. Support for such an amendment can be found throughout the instant specification, for example, page 29, lines 3-9:

> "As used herein the term genetically linked refers to a genetic distance smaller than 50 centiMorgan, preferably smaller than 40 centiMorgan, more preferably smaller than 30 centiMorgan, more preferably smaller than 20 centiMorgan, more preferably smaller than 10 centiMorgan, more preferably smaller than 5 centiMorgan, more preferably smaller than 1 centiMorgan, most preferably in the range of 0 to 1 centiMorgan, wherein 0 centiMorgan refers to juxtaposed sequences."

In contrast, Lee et al. teach the transformation of turfgrass with a gene of interest, and, optionally, a selectable marker gene, for **transient expression**:

> "The successful delivery of the DNA into a cell may be preliminarily evaluated by the transient expression of a "reporter" gene. A reporter gene is a component of the DNA used for transformation and may be the same as or different than the gene conferring another desired property."(Lee et al, page 12)

which may optionally be different from the transgene of interest. No tight genetic linkage between advantageous and mitigating traits is inferred or taught.

Thus, Lee et al fails to teach the essential features of a genetically engineered advantageous trait and a mitigating genetic trait genetically linked at a distance of no greater than 10 centimorgans, and transforming a population of plants of a cultivated crop to co-express the genetically linked advantageous engineered trait and mitigating trait, and as such cannot and does not anticipate the invention as recited in amended claim 1, and claims dependent therefrom of the present invention.

Thus, it is Applicant's strong opinion that amended claim 1, and claims dependent therefrom, now more clearly define the essence of the method of the

present invention, and as such overcome the Examiner's rejection thereof on the basis of the cited art references.

35 U.S.C. § 103(a) Rejections: MOGEN INTERNATIONAL (WO97/42326) in view of Christou et al (US. 6,114,603) and FORBIO RESEARCH (WO97/30162) in view of Boudet et al (US 5,451,514)

The Examiner has rejected claims 1-3, 7 and 8 under 35 U.S.C. § 103(a) as being unpatentable in view of MOGEN INTERNATIONAL (WO97/42326) in view of Christou et al (US. 6,114,603)(claims 1-3 and 7) and FORBIO RESEARCH (WO97/30162) in view of Boudet et al (US 5,451,514) (claims 1-3 and 8). Claims 2 and 3 have been canceled, rendering moot the Examiner's rejection thereof. Claim 1 has now been amended. The Examiner's rejections are respectfully traversed.

The Examiner has stated that MOGEN INTERNATIONAL teaches a method for producing a transformed, cultivated crop capable of mitigating the effects of introgression of at least one advantageous genetically engineered trait to an uncultivated interbreeding species related to the transformed cultivated crop as claimed in the subject claims. In particular, the Examiner alleges that MOGEN INTERNATIONAL does not prevent tight genetic linkage between the advantageous and the mitigating traits.

As described *supra*, Applicant has amended claim 1, from which the remaining claims subject to the rejection depend, to include the limitation of "...whereas said advantageous genetically engineered trait and said mitigating genetic trait having a genetic distance of no greater than 10 centimorgans from each other..."

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Further, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicant submits that the Examiner has failed to meet the burden to establish a *prima facie* case of obviousness of the claimed invention over MOGEN INTERNATIONAL, in view of Christou et al. as required *supra*.

For clarity, Applicants are describing the teachings of MOGEN INTERNATIONAL and Christou et al. individually, but are traversing the rejection with respect to the combination of these references, *infra*.

- MOGEN INTERNATIONAL teaches the transformation of plant cell with TPS and TPP, and the optional use of a selectable marker gene for identification of transformants. The marker and gene of interest do not have to be linked.
- Christou et al. merely teaches biolistic transformation of sugar beet plants with a gene of interest, and the optional use of herbicide resistance as a selectable marker of transformation.

The combination of MOGEN INTERNATIONAL and Christou et al. do not teach or suggest, explicitly or inherently, methods of mitigation of introgression of advantageous traits by co-transformation with a conditionally mitigating second genetic trait genetically separated by no greater than 10 centimorgans from one another. In combining MOGEN INTERNATIONAL and Christou et al, the Examiner asserts that MOGEN INTERNATIONAL does not prevent such a linkage, that "tightly linked" is a broad and circular definition and that such introgression could occur whether the two genes were on the same construct or not. However, it is well established that "in relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 49 USPQ2d 1949 (Fed. Cir. 1999). "In order to find

inherent anticipation, 'the undisclosed element of the prior art had to be a necessary technological fact of the prior art.' " *Continental Can Co. v. Monsanto Co.* 948 F.2d 1264, 20 U.S.P.Q.2d (BNA) 1746 (Fed. Cir. 1991). " It is inadequate to show that the prior art process would 'probably, or possibly, produce the undisclosed element.' " *Id.* **Rather, the undisclosed element had to flow as a natural consequence from the technological constraints of the prior art.** *Id.*

Therefore, "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993) (emphasis in original).

The basis in combining MOGEN INTERNATIONAL and Christou et al. with reasonable predictability is based on the Examiner's opinion that the tight genetic linkage and tandem introgression is not prevented . As such, Applicant submits that the Examiner has failed to meet the burden of establishing a *prima facie* case of obviousness.

One of ordinary skill in the art reading MOGEN INTERNATIONAL and Christou et al. in combination would not have known to link an advantageous genetically engineered trait with a conditionally mitigating trait in tight genetic linkage of 10 centimorgans or less, to ensure tandem introgression as required by the instant invention.

Applicant submits that MOGEN INTERNATIONAL in combination with Christou et al. do not teach or suggest the methods and compositions as described and claimed herein. Reconsideration and withdrawal are respectfully requested.

The Examiner has further stated that claims 1-3 and 8 are rendered obvious by FORBIO RESEARCH in view of Boudet et al. Applicant disagrees.

FORBIO RESEARCH teaches the identification and cloning of reproductive-organ specific promoter elements from eucalypts, and their introduction into constructs for transformation of eukaryotic organisms, particularly plants and trees, with sequences of interest. FORBIO RESEARCH is silent regarding the subject of accidental, undesirable transgene flow from the transformed plants, and methods and/or constructs for the mitigation of the effects thereof, and the essential feature of tight genetic linkage of no greater than 10 centimorgans between sequences for an

advantageous and a mitigating trait is specifically lacking. Thus, FORBIO RESEARCH, alone or in combination with any other references, does not and cannot render the constructs and methods for their use of the claimed invention, lacking in novelty or obvious.

Boudet et al. teach the use of construct including a plant promoter and a sequence encoding a lignin precursor in an antisense orientation, for the suppression, in trees, of lignin biosynthesis, with the intent of producing timber with improved paper producing potential. Like FORBIO RESEARCH, Boudet et al is silent regarding the subject of accidental, undesirable transgene flow from the transformed plants, and methods and/or constructs for the mitigation of the effects thereof, and lacks any mention of the essential feature of tight genetic linkage, no greater than 10 centimorgans, between such a lignin-suppressor sequence and mitigating sequences.

One of ordinary skill in the art reading FORBIO RESEARCH and Bouidet et al. in combination would not have known to link an advantageous genetically engineered trait with a conditionally mitigating trait in tight genetic linkage of 10 centimorgans or less, to ensure tandem introgression as required by the instant invention.

Applicant submits that FORBIO RESEARCH in combination with Boudet et al. do not teach or suggest the methods and compositions as described and claimed herein. Reconsideration and withdrawal are respectfully requested.

In view of the above amendments and remarks it is respectfully submitted that claim 1, and all claims dependent therefrom are now in condition for allowance. A prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Date: January 30, 2008

Enclosures:

- Petition for Extension (3 Months)
- Request for Continued Examination (RCE)